EXHIBIT 2

EXPERT REPORT OF DR. HENRY C. LEE

Terry Henry
Blank Rome
One Logan Square
130 North 18th Street
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February 20, 2020

Dear Terry Henry:

I have been asked to offer opinions regarding neonatal abstinence syndrome (NAS). In this report, I will discuss various aspects of NAS, including its development in neonates, diagnosis, treatment, and prognosis.

As discussed more fully below, NAS develops in some, but not all neonates whose mothers received opioids, the diagnosis of NAS is subjective and influenced by various factors, treating pregnant women who are taking opioids both illicitly and therapeutically is complex, and there is uncertainty as to both the short- and long-term management and prognosis of NAS. Furthermore, long-term prognosis in neonates exposed to opioids is influenced by many social and other medical factors.

I understand that Teva Pharmaceuticals USA, Inc. and other defendants in the NAS litigation may use my expert testimony in proceedings related to the NAS litigation.

I. QUALIFICATIONS

I am Associate Professor of Pediatrics at the Stanford University School of Medicine and a Fellow of the American Academy of Pediatrics. I am board certified in Pediatrics and Neonatal-Perinatal Medicine by the American Board of Pediatrics. I care for neonates in the well baby nursery, intermediate care nursery, and neonatal intensive care unit (NICU). In these settings at the Lucile Packard Children's Hospital Stanford, I care for neonates who may be suspected of having NAS and supervise the treatment of patients who have been diagnosed with NAS. I have worked in several other hospitals and NICUs in which I have also cared for patients with NAS and helped to develop protocols for their management.

I am the Chief Medical Officer of the California Perinatal Quality Care Collaborative (CPQCC). In that role, I coordinate quality improvement activities and research across 140 neonatal intensive care units. I am also a member of the Steering Committee of the California Maternal Quality Care Collaborative (CMQCC), which is concerned with data-driven quality of care for mothers across the state. These two organizations have been instrumental in reducing morbidities for mothers and newborns across California over the past decade. In these roles, I lead efforts across the state in selecting quality measures across hospitals for neonatal and maternal care, and then addressing gaps in quality of care by directing implementation programs and providing resources to hospitals to improve care.

A recent project of CPQCC and CMQCC, the Mother & Baby Substance Exposure Initiative, is specifically concerned with addressing the needs of mothers and neonates affected by opioid use disorder:

https://www.cpqcc.org/improvement/projects/substance-exposure/mother-baby-substance-exposure-initiative

I am a leader of this statewide project implementing best practices for community and hospital-based care for affected patients. I and co-authors recently published a study on current practices surrounding NAS in California hospitals.(1) I give educational talks to clinicians on management of NAS.

I have authored more than 135 peer-reviewed research papers, many which concern assessment of clinical practice in medical care for mothers and newborns.

Other qualifications are noted on my CV. I have never testified as a witness at trial. I have testified at 3 depositions. I am being compensated at a rate of $700/hour.

II. BACKGROUND ON NAS

In medical terminology, a syndrome is distinguished from a disease in that syndromes are a constellation of symptoms that may not always have a definite cause.(2) A disease, on the other hand, is a condition in which a causative agent or process is well established with high degree of certainty by the medical community. In that vein, NAS is a syndrome, describing a constellation of symptoms and signs that are transiently noted in the neonate after birth following discontinuation of drugs used by the mother during pregnancy.(3, 4) These symptoms include neurologic abnormalities such as tremors and hypertonia, autonomic instability such as sweating and sneezing, and gastrointestinal disturbances such as diarrhea and vomiting. Opioids such as heroin, oxycodone, and methadone are associated with the potential for NAS developing in the chronically exposed neonate. During pregnancy, non-opioid drugs, such as cocaine, amphetamines, antidepressants (selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants) and benzodiazepines are also associated with NAS potentially developing in the neonate.(5-7) These symptoms can also be exhibited in neonates undergoing withdrawal from nicotine / tobacco.(8, 9) Some neonates with NAS will require treatment with medications, while some will not require medications. Ultimately, the symptoms of NAS will resolve in the neonatal period, whether or not specific treatment is provided. This resolution may take place over a period of days to several weeks.

The term neonatal opioid withdrawal syndrome (NOWS) is used to distinguish a patient who has been identified to have opioid-only withdrawal symptoms.(10) For pregnant women who are addicted to opioids, i.e. having opioid use disorder (OUD), the most appropriate treatment is to enter into Medication Assisted Therapy (MAT), wherein the patient is transitioned to taking buprenorphine or methadone.(11) While neonates born to women who are taking methadone or buprenorphine may have NAS, the symptoms observed are generally more moderate than if the woman was taking other opioids, particularly if they were taking opioids long-term. After delivery, the neonate at risk for NAS would generally be admitted to the well baby nursery or room with the mother in the postpartum unit. Not all neonates exposed to opioids in utero will develop NAS.(12, 13) Due to the uncertainty of development of NAS based on the exposure of the fetus, neonates who are at risk can be monitored after birth for development of symptoms.

Neonates identified as having NAS can be treated with non-pharmacologic treatment, while those who continue to have symptoms may receive pharmacologic treatments such as morphine or methadone. While morphine and methadone are opioids, these drugs are used to treat NAS regardless of the exact drug that the fetus was exposed to, as they treat the symptoms for a variety of withdrawal symptoms. These drugs will reduce irritability, jitteriness, and other symptoms of NAS, regardless of the underlying cause. Traditionally, phenobarbital was used for NAS, and similarly, clonidine is now an adjunct treatment for NAS, although neither are opioids. The relief of symptoms by these drugs do not necessarily confirm a diagnosis of NAS, nor do they pinpoint which drug of fetal exposure is causing the withdrawal symptoms. The course of treatment varies from individual patient to patient. An important component of treatment is frequent assessment of the neonate in order to gauge the most appropriate therapy, which may evolve with the clinical course. Arrangement of close follow-up after going home is important for both mother and baby, as would be the case for all newborns, but with attention to the possibility of symptoms reappearing after discharge. This specific concern would decrease after the first few weeks after birth.

III. DIAGNOSIS OF NAS

NAS is a condition that describes a constellation of symptoms and signs that are noted in the newborn period. As previously noted, it can be caused by opioids used during pregnancy or other drugs such as antidepressants. Diagnosis depends on history (or suspected history) of maternal drug use (such as opioid use disorder) and neonatal findings consistent with NAS.(10) The diagnosis of NAS requires history of drug use during pregnancy. There would not be a physiologic withdrawal present, for example, if a mother who had been using drugs prior to pregnancy, stopped after she became pregnant. It would not be possible to distinguish in circumstances of multiple drug use, including tobacco, nicotine, or marijuana, which of these substances would be manifesting as symptoms of withdrawal in the infant identified with possible NAS. Identification of a neonate strictly as NOWS (opioid only withdrawal symptoms) would require a thorough assessment of the pregnancy to assess the full range of maternal exposures, including timing and duration of various exposures. Other neonatal problems can manifest similarly to NAS, such as seizures due to other causes, sepsis (infection), and hyperthyroidism.(10) Tests to rule out such conditions may be warranted if the causes of symptoms are unclear. Some clinical findings, such as sneezing, nasal congestion, tremors, jitteriness, increased respiratory rate (tachypnea), and difficulty feeding may be aspects of normal newborn behavior that will resolve on their own.

There is not a standardized accepted method of diagnosis of NAS.(14, 15) The most common tool for assessing newborns and a method of diagnosis of NAS is a modified version of the Finnegan Neonatal Abstinence Scoring System.(14) This form contains signs and symptoms as follows: excessive cry, sleep duration after feeding, hyperactive Moro reflex (a newborn neurologic reflex), tremors, increased muscle tone, excoriation, seizure, fever, sweating, nasal stuffiness, sneezing, increased respiratory rate, poor feeding, vomiting, loose stools, failure to thrive (poor weight gain), and irritability.(10) A typical use of the Finnegan score is to measure scores over the first 2 to 3 days after birth, and the diagnosis of NAS occurs when there are three consecutive scores of 8 or higher, or two consecutive scores of 12 or higher.(16) As noted by the above signs and symptoms,

an assessment of a baby with a complete physical examination and review of findings would be important to make a diagnosis of NAS over a period of time. Because some of the signs that compose the Finnegan score may be normal variation of a neonate's course, one high score may not indicate a diagnosis of NAS.

A major component of the Finnegan score is measurements that relate to irritability and neurologic symptoms. While these can occur from withdrawal from opioids, they are also seen after withdrawal from other substances such as nicotine, benzodiazepines, and antidepressants. Thus, while a diagnosis of NAS could be based on withdrawal from opioids, it is often due to another substance or combination of opioids and other substances. In some cases of maternal opioid use, it is possible that the Finnegan score may have been at a level that would not have led to concern, but due to the addition of other substances, the Finnegan score may be pushed to a higher level that leads to a diagnosis of NAS.

Although it is commonly used, the Finnegan tool has been questioned as whether it is appropriate for this purpose, due to lack of validation, lack of correlation to improving outcomes, and the lack of consistency and accuracy.(17, 18) Ultimately, the tool relies on a combination of subjective measurements and objective measurements that can be inconsistent based on timing and provider judgement. The timing of the assessment plays a role in diagnosis, and yet is typically not standardized.(17, 19) For example, one component of the score is yawning, and it has been pointed out that a neonate that yawns four times in a period vs. three times could push a neonate to be assessed as having NAS vs. not and requiring treatment.(20) Newer approaches have abandoned the Finnegan score in favor of assessing functional parameters such as the "Eat Sleep Console" method.(21) This approach assesses whether a neonate can feed adequately, sleep for at least one hour, and can be consoled within 10 minutes. It is not clear whether this is a more effective tool for diagnosis of NAS.

Unlike most medical conditions for which there is a gold standard diagnostic test such as a blood test, a urine test, or radiologic test, there are multiple potential tools for assessment for NAS, and all of these assessments consist of a clinician subjectively evaluating the neonate. While the Finnegan scoring system is widely used, there are variations of the Finnegan, other methods proposed by Rivers, Lipsitz, the Neonatal Narcotic Withdrawal Index and newer methods such as "Eat Sleep Console".(21-26) Ultimately, there is wide variation and not a consensus on how to diagnose NAS.

A critique of all of these assessment tools is that the various elements of scoring are subjective. For example, the Finnegan score has components that ask a clinician to distinguish the character of a cry as excessive or inconsolable, whether tremors are mild or moderate to severe, increased muscle tone, has poor feeding, or excessive irritability. Training clinicians may help to develop consistency, but effects of training do not persist over time, with the biggest discrepancies in assessing neurologic symptoms.(18)

The clinician may be motivated externally to make a diagnosis of NAS if they believe that this will facilitate other actions for the neonate and family. For example, the Child Abuse and Prevention Treatment Act requires that Child Protective Services is notified when a neonate experiences withdrawal symptoms from prenatal drug exposure.(27) In some cases, a diagnosis may facilitate the provision of other health care and social services for

families that may benefit from these services for a variety of reasons. Because many neonates that have prenatal drug exposure are also exposed to other social and medical risks during pregnancy and after birth, the clinician may be biased toward diagnosing NAS, particularly in those cases which are borderline or even fails to meet criteria. In one analysis of Medicaid claims data of neonates diagnosed with NAS and a review of their corresponding medical records, 24% were patients that did not require pharmacologic therapy, and on review of medical records, 9% of cases labeled as NAS did not have documentation that would meet clinical criteria of NAS.(28)

IV. USE OF OPIOIDS DURING PREGNANCY

It is well recognized that opioid use in the United States has increased over the past 2 to 3 decades. Opioids are a legitimate class of pain medications and can be prescribed appropriately to a variety of patients both inpatient and outpatient. This includes women who are of childbearing age. In this context, women who use opioids for pain relief and/or women who are dependent on or addicted to opioids become pregnant. Furthermore, some women may start or re-start opioid use during pregnancy. Treating any patient with an opioid use disorder can be difficult, due to the nature of physical dependence on the drug. Treating a pregnant woman with opioid use disorder is even more complex and challenging, as a woman undergoes physiologic changes throughout pregnancy, including varying metabolism and clearance of medications, as well as the implications for maternal drug use on the growing fetus.

In a statement by the American College of Obstetrician & Gynecologists (ACOG), the main organization representing obstetricians in the U.S., it is noted that there are “unique needs of pregnant women with an opioid use disorder,” and therefore, that “…health care providers will need to consider modifying some elements of prenatal care …in order to meet the clinical needs of the patient’s particular situation.”(11) For those women who were taking opioids prior to pregnancy or started during pregnancy, this individualized care in many cases means continuing medications of some sort during pregnancy is recommended.(11) According to ACOG, medically supervised withdrawal during pregnancy is not preferred, due to the risk of worse outcomes. Stopping opioids abruptly carries a higher risk of relapse to higher risk opioids. The World Health Organization also advises against opioid detoxification during pregnancy and recommends a treatment program with either methadone or buprenorphine.(29) Methadone is an opioid that is similar to morphine or heroin, but longer lasting and with less euphoric properties, which also creates a dependence for the user. Buprenorphine is an opioid partial agonist. This means that it acts on opioid receptors similar to morphine and heroin, creating similar physiologic effects, but with weaker strength. Both methadone and buprenorphine may lead to NAS in the newborn.

Methadone is usually administered and dispensed on a daily basis as part of a comprehensive treatment program. Treatment with buprenorphine can be provided with self-administration. Therefore, patients who are at higher risk of inappropriate use of drugs may not be good candidates for buprenorphine.(30) It is recommended that women who are already receiving methadone should not transition to buprenorphine due to risk of withdrawal.(11)

For those patients during pregnancy who experience pain, such as lower back pain particularly in late pregnancy, opioids may be considered reasonable for treating pain without harm to the fetus.(31, 32) While caution should be exercised in order to avoid dependence, treatment of pain is an important aspect of medical care for pregnant patients. ACOG recognizes that while opioids should be limited or avoided during pregnancy if possible, that it is part of the regimen of treating pain during pregnancy.(11)

Opioid pain medications are used to treat pain in a variety of conditions. Just as with conditions outside of pregnancy, judicious and appropriate use of opioid medications can be an effective to relieve both acute and chronic pain. On the other hand, opioids can lead to physiologic dependence in both pregnant and non-pregnant patients. Therefore, patients who receive opioid medications during pregnancy should be closely followed, similar to non-pregnant patients. During labor and delivery, opioids may also be used by healthcare providers in order to relieve pain. Opioids such as fentanyl, remifentanil, meperidine, and morphine are commonly used in this setting for pain relief.(33) While these opioids, just as other medications, may occasionally have adverse effects, they are considered safe in the labor and delivery setting with close monitoring of the mother and fetus or infant.

V. RISK OF DEVELOPMENT OF NAS

Not all neonates born to mothers who have taken opioids during pregnancy develop NAS. As noted above, some mothers will receive opioid medication for short courses to relieve pain either during pregnancy or during the labor and delivery process. The neonates born to these mothers would not be at risk for NAS. The quantity, duration, dosage, and type of opioid taken are all influential factors for the potential risk of NAS and the severity of NAS if it develops. For example, studies have shown that while some neonates who have been exposed to buprenorphine may develop NAS, that the symptoms are generally more moderate than if the mother had been on methadone treatment.(34) Even some infants born to mothers who have been on opioids long-term will not have NAS. Therefore, protocols are in place to monitor infants born to mothers with known history of long-term opioid use, but not to automatically treat them for NAS.

There is not clear evidence on an exact duration of drug use, or timing of drug use and impact on potential development of NAS. However, from my experience in caring for babies with NAS or babies who have been sick or preterm and exposed to opioids in the NICU for pain / discomfort, it is clear that withdrawal symptoms will fade over the course of days or weeks. Therefore, if a woman were to use opioids in the first or second trimester and then stop, it would be highly unlikely that a baby born at term in that situation would develop NAS.

Women who are using other substances in addition to opioids, such as nicotine, benzodiazepines or psychotropic medications such as antidepressants (selective serotonin reuptake inhibitors), are more likely to have neonates that have NAS; these same chemicals and drugs increase the incidence and severity of NAS.(35, 36) Mothers who received polypharmacy may have neonates 10 times more likely to require medical treatment for NAS.

Maternal dose of methadone has been shown to affect the length of hospitalization for treatment of NAS, with higher doses in the third trimester in particular affecting length of

stay.(37-40) While some studies have not found a relationship between dosage and NAS outcomes, the absence of a finding in one study may be due to small sample size of the patient population or not enough differences in dosage. The presence of positive findings in multiple studies, as well as the logic of increased dosages and potency of medications affecting the dependence of both the mother, and potentially the development of NAS and its severity when present in neonates, makes physiologic sense. Just as the type of opioid, the duration of therapy, and dosages will be risk factors for an adult developing opioid use disorder, a similar phenomenon would be at work for fetuses and neonates. Furthermore, the same medication regimen in one adult can lead to opioid use disorder in one person, but not another. Therefore, individual genetic predisposition also plays a role in the development of NAS.

Preterm infants are often treated with opioids for pain treatment in NICUs. Neonates, including those who are preterm or those requiring surgery and receiving procedural interventions, experience pain, and part of my role as a neonatologist is to prevent and control pain. Standard drugs in pain control and management in the NICU include fentanyl and morphine, which are opioid drugs.(41) Based on the clinical scenario, the drug, dosing, and duration of treatment will vary. Some neonates in the NICU may receive just one or a few doses of opioid for pain control, while others may receive continuous infusions for days or weeks. Just as with any drug, there are potential adverse effects of opioids, but they are an effective treatment that can be used to treat pain or discomfort.

Infants in the NICU who receive opioids long-term may develop a physiologic dependence similar to older patients. This dependence is variable according to patient, but would be related to the type of drug, dosage, and duration of treatment. A growing fetus, similar to a preterm infant in some ways, would have a similar risk profile of development of NAS based on the type of drug, dosage, and duration of treatment of the mother. There may be even more variability in this population, as maternal factors such as timing of opioid use, polypharmacy, nutrition, and overall health, will also play an important role in fetal health. Therefore, the assessment and potential care of an infant exposed to opioids must be individualized. Ultimately, although opioids, when used in neonates, may have adverse effects such as respiratory depression or delayed feeding in the immediate period, there is no evidence to suggest that it alters long-term outcomes such as development.(41)

VI. FOLLOW UP CARE AND LONG TERM EFFECTS OF OPIOID EXPOSURE

I am currently engaged in a statewide collaborative project in California in order to improve care for infants affected by NAS. In this effort, we recommend good communication between hospital providers taking care of mothers and infants affected by NAS with the outpatient primary care provider. Each family may have circumstances that require assessment for other services, but the care for infants with NAS is in many ways similar to that of healthy newborns not affected by NAS, such as ensuring adequate feeding, and support of breastfeeding. There would also be continued assessment for potential symptoms of withdrawal. This would be provided by the primary care provider and the concern for this would decrease over time over the ensuing weeks. Some mothers who continue to have opioid use disorder may be referred to treatment programs. Ultimately, services are in place in order to care for both mothers and infants affected by opioid use disorder and NAS. Our main effort in the state collaborative project is to educate providers about NAS and connect hospital providers to existing outpatient providers. These

services, both inpatient and outpatient, are covered by insurance, both private and public (government). The American Academy of Pediatrics clinical report on neonatal drug withdrawal recommends, "After discharge, outpatient follow-up should occur early and include reinforcement of the education of the caregiver about the risk of late withdrawal signs."(42) This care can be provided by a pediatrician or similar health care provider. It is not clear that new programs are needed in order to care for this population.

Due to the increase in opioid use disorder, there is increased interest and progress on research on NAS. Research on the long-term effect of opioid exposure in utero is being performed, but the actual impacts on individual patients are largely speculative. In an expert panel meeting in 2018 of the National Institutes of Health, which is the largest funder of biomedical research in the U.S., it was noted that, "…we do not know what the long-term implications of early exposure to opioids (or to medications used to treat opioid use disorder) will be."(43) While some studies have associated opioid use of the mother to adverse outcomes in their children, these are observational studies with potentially confounding factors that are hard to tease apart. The type of study that is generally used to establish a cause-effect relationship in medicine, the randomized controlled trial, would not be ethical to answer this question, as we would not want to randomly assign mothers to get opioids. Therefore, studies that have investigated this issue have been observational.

It is important to recognize that in this context, patients who use opioids during pregnancy represent a diverse group, and it is important to recognize and differentiate between opioid use in the context of medical care, opioid misuse, and untreated opioid use disorder.(11) The prenatal risk factors that are already well established for behavioral and cognitive outcomes in children include issues such as maternal prenatal care, maternal mental health conditions such as depression or anxiety, socioeconomic status, education, risky behaviors, alcohol, and tobacco use. These factors are often present in women who use opioids, and therefore, it is difficult to tease out the individual impact of each of these factors in observational studies.(44) A large study in Pennsylvania found that children with in utero opioid exposure had the same probability of having a pediatric complex chronic condition similar to children who had tobacco exposure without opioid exposure, and also those with neither exposure.(45) Those who had formally been diagnosed with NAS also did not have significant difference long-term compared to those exposed to opioids in utero without a diagnosis of NAS.

Ultimately, the studies that have been performed on cognitive development in opioid exposed infants have been unclear as to effect. Infants exposed to methadone in utero, when compared to infants with similar age, race, socioeconomic status, had similar cognitive scores.(46) The factors that occur after an infant is born, such as supportive home environment, parenting, early exposure to books and positive stimuli, are more likely to influence cognitive and other development in infants exposed to opioids than the occurrence of opioid exposure in utero.(11, 46)

VII. REVIEW OF DR K. ANAND'S REPORT

I have reviewed Dr. Kanwaljeet Anand's report prepared for this case. There are some aspects of Dr. Anand's report that I agree with and some points with which I have some

disagreement. I will not comment on every aspect of his report, but comment on some key agreements and disagreements here.

On page 2, I agree when Dr. Anand notes that there are many different ways to diagnose NAS, such as Finnegan scoring, modified versions of the Finnegan score, Rivers tool, and Lipsitz score. He also notes that, while a quality improvement initiative increased consistency of Finnegan scoring by nurses, that the "…effects of this training were short-lasting." I agree that the diagnosis of NAS is challenging due to the various tools, none of which are considered a gold standard, involve subjectivity, and are not easy to use, even after dedicated training through a quality improvement effort.

On page 2, I agree when Dr. Anand notes that not all children born to birth mothers suffering from opioid use disorder in pregnancy will show signs and symptoms of NAS.

On page 4, Dr. Anand notes that NAS is associated with premature birth, low birth weight, intrauterine growth retardation, perinatal or neonatal mortality, increased birth defects, delayed cognitive development, long-term behavioral problems, and other issues. While some studies have shown associations of NAS to some of those conditions, these are not conclusive findings, and a causative effect is not proven. I disagree with the notion that we know that a direct causal relationship exists between the cause of NAS and the cause of these conditions. First, the studies on these outcomes are inconclusive as to the consistency of these findings. Second, while it is possible that opioid exposure may have contributed to a few of these outcomes, in general, the preponderance of other risk factors that are also associated with opioid exposure are more likely to have been the direct cause than opioid exposure. Such factors include other substances, the socioeconomic circumstances of the family, and other social factors.

Specifically in regard to congenital defects, a systematic review in 2017, which is a comprehensive literature review on this subject, found that while there were some potential associations, that the available literature on this subject was limited in strength. They noted, "We have considerable concerns regarding the quality of the studies included in this review. There were no randomized controlled trials and few high-quality observational studies that evaluated the association between prenatal opioid use and congenital malformations."(47) Furthermore, they noted that most studies on this topic were published prior to 1999, when patterns of opioid use were different than the current era.

On page 6, Dr. Anand cites a systematic review and meta-analysis of cohort studies on prenatal opioid exposures and neurocognitive outcomes. I disagree with Dr. Anand that this study leads to a conclusion of causal relationship. The study reports an association of opioid exposure and cognitive outcomes. However, the authors themselves note the limitation of their study in drawing a causal relationship, noting that "In addition, the cause of these poor outcomes cannot be absolutely determined from the studies reviewed herein owing to the combination of inherited epigenetic changes, poor parental education, direct effect of opioids on brain volume, or the child's home environment."(48)

I agree with Dr. Anand when he notes the importance of home environment in developmental outcomes, citing another study and noting that children identified with NAS who are discharged home with their birth mother are more likely to be referred for early intervention services than those placed in foster care.(49)

In fact, Dr. Anand's own research reflects that social and environmental factors play a critical role in physical and mental health, such that the conclusions reached in his report on the key role of NAS and later health are inconsistent. He is the lead author on a recent paper describing research on more than 1500 pregnant women, in which he and co-authors researched how socioeconomic adversity in childhood is associated with negative impact on physical and mental health, as well as school performance.(50) He reported that significantly worse health and social outcomes occurred with their assessment of worse socioeconomic adversity index, with the main contributors to this index being factors such as parental income, household structure, marital status, and education. Maternal drug abuse was also associated with higher risk of socioeconomic adversity. Ultimately, I agree with the findings of this study, that social and environmental factors are likely to play a critical, and often predominant role, in childhood health and development.

I agree with Dr. Anand when he notes on page 8, "Despite the recent flurry of scientific publications on this topic, there are numerous unanswered questions about the epidemiology, risk factors, diagnoses, management, and responses to therapy in the children with NAS." I agree with this statement, that there are more questions than answers at present in regard to many aspects of NAS, including diagnosis, and long-term outcomes. It is premature to declare that we know how opioids affect all opioid exposed infants; that we can generalize about cases without knowing the specifics of each case, learning about the maternal and neonatal history, examining the infant, and following their course both in the hospital and after discharge. Each case of opioid use in pregnancy is very different.

VIII. CONCLUSION

In conclusion, NAS is a condition that can occur with prenatal exposure to opioids. The type, duration, dosage, and timing of exposure to opioids, the inherent predisposition of the mother and fetus, and other factors such as socioeconomic condition, maternal mental health status, the presence of other substances, all have an influence on whether the baby will have NAS after birth, if they do have NAS, and the severity of the condition. The diagnosis of NAS is challenging and inconsistent across providers and healthcare systems. There may be other motivating factors for NAS diagnosis including the ability to access increased services. The long-term effects of NAS are uncertain and research on this topic is limited by its observational nature and the large numbers of other factors which confound the potential causal relationship, such as home environment and other maternal risk factors that impact development.

I hold the opinions that I have expressed in this report to a reasonable degree of medical certainty.

Sincerely,

Henry C. Lee, MD